UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

MEMORANDUM

Date: 15-AUG-2013

SUBJECT: **Chlorpropham:** Summary of the Hazard and Science Policy Council (HASPOC) Meeting of August 1, 2013: Waiver for the Immunotoxicity Study (870.7800).

PC Code: 018301
Decision No.: N/A
Petition No.: N/A
Risk Assessment Type: N/A
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MRID No.: N/A

DP Barcode: N/A
Registration No.: N/A
Regulatory Action: N/A
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40 CFR: N/A

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THROUGH: Jess Rowland, Co-Chair
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TO: Anwar Dunbar Ph.D., Pharmacologist
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MEETING ATTENDEES:

HASPOC Members:	Anna Lowit, Elissa Reaves, Elizabeth Mendez, Jeff Evans, Jeff Dawson, Jonathan Chen, Michael Metzger, P.V. Shah
Presenter:	Anwar Dunbar
Other Attendees:	Chris Schlosser, Jaime D'Agostino, Monique Perron, Yung Yang, Joey Bever, Ana Rivera-Lupianez, Uma Habiba, Jonathan Leshin, Kristin Rury, Julie Van Alstine

I. PURPOSE OF MEETING

In the most recent scoping document for chlorpropham, a guideline immunotoxicity study was listed as a data gap in accordance with the revised CFR Part 158 (A. Dunbar, *et al.*, 22-Nov-2010; D378551). Pace International and the Chlorpropham Task Force have recently submitted a waiver request for a chlorpropham guideline immunotoxicity study (See Pace DCI Response, 13-Jun-2010). The HASPOC recently concluded that a subchronic inhalation toxicity study and acute and subchronic neurotoxicity studies for chlorpropham were not required (TXR# 0056597). The toxicology database for chlorpropham is adequate except for the required guideline immunotoxicity study (870.7800). The HAPOC met on August 1, 2013 to discuss the need for an immunotoxicity study for chlorpropham.

II. SUMMARY OF USE PROFILE, EXPOSURE, AND HAZARD CONSIDERATIONS

a. Use Profile: Chlorpropham (isopropyl *m*-chlorocarbanilate or CIPC) is a carbanilate herbicide and plant growth regulator. Chlorpropham was first registered in the U.S. in 1962 as a pre-emergence and post-emergence herbicide to control annual grasses and many broadleaf weeds. It was also used as a plant growth regulator on a variety of terrestrial food crops, nonfood crops, ornamentals, and stored potatoes (EPA, 1996). By 1990, the primary registrants dropped all nationwide uses of chlorpropham except for sprout control on post-harvest stored potatoes. Chlorpropham is currently registered for use as a plant growth regulator to inhibit sprouting of stored potatoes. It is also registered under a state and local needs registration (SLN) for use on ginkgo trees in the District of Columbia (D.C.) and for field-grown Easter lilies in California and Oregon (BEAD Chemical Profile for Registration Review: Chlorpropham, 05-Jun-2010, K. Stebbins, *et al.*).

b. Toxicity Profile: In the subchronic and chronic toxicity studies in rodents and non-rodents, the hematopoietic system and the thyroid glands were the target organs for chlorpropham-induced toxicity. Changes in the hematopoietic system mainly manifested as anemia. Anemia due to red blood cell destruction and a response to synthesize increased red cells were the prominent effects. In dogs following exposure for 60 weeks, histological changes in the thyroid glands consisted of irregular shaped follicles lined by medium- to high-cuboidal epithelium, and the presence of clear to pale staining colloid. Dogs in the 350 or 500 mg/kg/day groups also had statistically significant decreased levels of the thyroid hormones, T_3 and T_4. There are no residual uncertainties for pre- and/or postnatal toxicity. Chlorpropham is classified as a Group E Chemical (evidence of non-carcinogenicity in humans; however, however, some chlorpropham is metabolized to 3-CA in potatoes). The Metabolism Committee stated that the dietary risk assessment for cancer should include this metabolite. This cancer dietary risk assessment should be performed using the Q_1* associated with 4-chloroaniline. The Committee recognized that this latter assumption may overestimate the risk associated with 3-CA, but believed that no reliable information exists at this time to refute this assumption. The Q_1* for 4-CA is 1.12×10^{-1} $(mg/kg/day)^{-1}$ (Memo, L. Brunsman, *et al.*, 14-Jul-2001; TXR 0014583).

c. Indicators for Potential Immunotoxicity

Parameter	Findings
Hematology Indicators (WBC changes)	None
Clinical Chemistry Indicators (A/G Ratio)	None
Organ Weight Indicators (Spleen, Thymus)	None
Histopathology Indicators (Spleen, Thymus, Lymph nodes)	Some hemosiderosis in the spleen and increased extra medullary hematopoiesis of the spleen and cellularity and erythropoiesis of the bone marrow, enlarged and darkened spleen
Toxicity Profile (Target Organs)	The thyroid and the hematopoietic system (effects indicative of a mild anemia)

d. Evidence for Immunotoxicity for SAR Chemicals –Retrospective Analysis: In considering the need for an immunotoxicity toxicity study, the Agency will evaluate other pesticides which share the same mode of action (MOA) and/or are in the same class. These pesticides can provide important information with respect to potential immunotoxic effects. Specifically, if other similar pesticides show immunotoxicity studies to be more sensitive, an immunotoxicity study may be required, depending on the exposure profile. Chlorpropham is a carbanilate fungicide which functions as plant growth regulators. According to HED's Integrated Structure, Toxicology, Endpoints and Properties (ISTEP) database, there are no immunotoxicity studies available for chemicals within this class.

e. Risk Assessment Considerations: In the most recent risk assessment, the acute reference dose (aRfD) for females 13-49 years old was based on a no-observed adverse-effect level (NOAEL) of 250 mg/kg/day, and the lowest-observed adverse-effect level (LOAEL) was 500 mg/kg/day based upon increased resorptions and post implantation loss in the rabbit developmental toxicity study. The chronic reference dose (cRfD) was based on a NOAEL of 5 mg/kg/day and LOAEL of 50 mg/kg/day based on increased thyroid weight and histopathological changes in both sexes, statistically significant decreases in thyroxine (T_4) levels seen at week 14 in males from the chronic dog study. The Cancer Peer Review Committee classified chlorpropham as a Group E chemical (evidence of non-carcinogenicity in humans).

The most recent food-only dietary-exposure assessment was conducted in 2002 using DEEM™ version 7.73 (Memo, D. Drew, *et al.*, 25-Feb-2002; D280798). The unrefined acute dietary assessment for females 13-49 years old resulted in exposure estimates that utilized 4% of the acute population-adjusted dose (aPAD). A partially refined chronic dietary exposure assessment was performed using pesticide data program (PDP) monitoring data for potatoes and milk and anticipated residues derived from feeding studies for other livestock commodities. Chronic dietary exposure estimates utilized 4%

of the chronic population-adjusted dose (cPAD) for the general U.S. population and 10% of the cPAD for children 1-6 years old, the most highly exposed population subgroup.

III. STUDY WAIVER REQUESTS:

The HASPOC recommends that a waiver can be granted for an immunotoxicity study for chlorpropham, based on the following considerations:

- The target organs for chlorpropham are the thyroid and the hematopoietic system, and effects are indicative of a mild anemia.

- The toxicology database for chlorpropham does not reveal any evidence of treatment-related effects on the immune system. The overall weight of evidence (WOE) suggests that this chemical does not directly target the immune system.

- Acute and chronic dietary exposure estimates for chlorfenapyr indicate no risks of concern for the general U.S. population or other population subgroups.

- Points of Departures (PODs) from the most sensitive endpoints are currently used for assessing risks from acute (developmental effects), short and intermediate (offspring effects), and long term (respiratory system) inhalation exposures.

All these factors indicate that an immunotoxicity study would most likely not result in an adverse effect that could be used as an endpoint for chlorpropham risk assessment.

IV. HASPOC CONCLUSIONS:

The HASPOC concludes, based on a WOE approach, that an immunotoxicity study is not required for chlorpropham. An immunotoxicity study is not anticipated to provide a lower point of departure or result in a more sensitive endpoint than those already used for chlorpropham risk assessment.